PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference -	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/IB 03/03936	International filing date *(day/month/year)* 25.07.2003	Priority date *(day/month/year)* 02.08.2002
International Patent Classification (IPC) or both national classification and IPC C12N9/12		
Applicant PROTEUS et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 3 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
19.02.2004	28.10.2004
Name and mailing address of the international preliminary examining authority: European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized Officer Lejeune, R Telephone No. +31 70 340-2347

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/IB 03/03936

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-21 as originally filed

Claims, Numbers

1-20 received on 04.08.2004 with letter of 04.08.2004

Drawings, Sheets

1/4-4/4 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☒ the claims, Nos.: 21

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-20
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-20
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-20
	No:	Claims	

2. Citations and explanations

   see separate sheet

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

The following document/s (D) is/are referred to in this communication; the numbering will be adhered to in the rest of the procedure:

D1: WO 98 22615 A (LIFE TECHNOLOGIES INC) 28 May 1998 (1998-05-28)
D2: KIM DONG-MYUNG ET AL: BIOTECHNOLOGY AND BIOENGINEERING, vol. 74, no. 4, 20 August 2001

D1 discloses methods to enhance nucleic acid synthesis by preventing the build-up of pyrophosphate. One of the methods (see example 2) consists in the addition to the reaction medium of yeast ATP-sulfurylase and adenosine 5' phosphosulfate (APS). The enzyme catalyses the formation of ATP and sulphate from APS and pyrophosphate.

D2 discloses different methods to regenerate ATP during cell free protein synthesis, using different glycolysis intermediates.

Novelty (Art 33(2) PCT)

Claim 1 is directed at a method to enhance the synthesis of proteins in a cell free system, where the system is enriched in ATP-sulfurylase. The prior art does teach the use of ATP-sulfurylase in a cell free system (see D1), but not for the synthesis of proteins. Therefore, the subject matter of claim 1 (and dependent claims 2-8) is new.

Claim 9 and 15 are directed at a cell-free system or a cell-free extract, containing components that are capable of translating mRNA encoding a desired protein, enriched with ATP-sulfurylase. The prior art does not teach ATP-sulfurylase enriched extracts where a working machinery for protein synthesis is present. Therefore, the subject matter of claims 9 and 15 (and dependent claims 10-14, 16-20) is new.

Inventive step (Art 33(3) PCT)

The subject matter of claims 1-20 is new and involves an inventive step for the following reasons:

The problem addressed by the application is the provision of a method to enhance in vitro protein synthesis in cell-free systems. The solution provided by the application is a method which comprises the enrichment of the cell-free system with ATP sulfurylase and its substrate adenosine 5' phosphosulfate, such that ATP is formed. Document D2, regarded as the closest prior art, discloses methods to enhance in vitro protein synthesis in cell-free systems by regeneration of ATP using glycolysis intermediates. In the light of D2, the remaining problem to be solved is to provide a further method to generate ATP. The solution is the use of ATP sulfurylase and adenosine 5' phosphosulfate. The use of this enzyme and its substrate in a cell-free system is known from D1.

The skilled person, when faced with the problem of providing a further ATP generating method for an in vitro protein synthesis system would not combine the teachings of D1 (the method to regenerate ATP for protein synthesis) with the method of D2 (use of ATP sulfurylase and APS during nucleic acid synthesis). Therefore, claims 1-20 do involve an inventive step.